N-ACYLPHOSPHORAMIDITES AND THEIR USE IN OLIGONUCLEOTIDE SYNTHESIS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to the synthesis of oligonucleotides, and intermediates useful in the synthesis thereof.

BACKGROUND OF THE INVENTION

Since the development of efficient and reliable methods for automated synthesis of oligonucleotides, and early observations about the potential therapeutic application of oligonucleotides, there is a high demand for new oligonucleotide analogues. This demand is due to the fact that natural oligonucleotides undergo very rapid nucleolytic degradation to monomeric nucleosides and nucleotides in biological fluids *in vitro* and/or *in vivo*.

The therapeutic application of oligonucleotides is based on the selective formation of hybrids between antisense oligonucleotides and complementary nucleic acids, such as messenger RNAs (mRNAs). Such hybrids inhibit gene expression by blocking protein translation. Successful inhibition of gene expression, however, requires the antisense oligonucleotide to be nuclease resistant so that it can be transported through biological membranes and can hybridize selectively to a target complementary nucleic acid, thereby actively blocking protein translation. Among the diverse oligonucleotide analogues that have been tested for antisense activity, those bearing phosphorothioate internucleotide linkages are the most nuclease resistant and, therefore, are the most widely used.